original research report

Epidemiological and mycological characteristics of candidemia in patients with hematological malignancies attending a tertiary-care center in India

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BACKGROUND AND OBJECTIVES: We undertook the present study to ascertain the contributing risk factors and explore the epidemiological and mycological characteristics of opportunistic candidemia among patients with hematological malignancies.
DESIGN AND SETTINGS: Observational cross-sectional study in a tertiary care center.
PATIENTS AND METHODS: Consecutive patients with hematological malignancies reporting to the collaborating medical and pediatric units with a febrile episode were recruited and screened for candidemia by blood culture. Recovered Candida isolates were speciated and antifungal susceptibility testing was performed as per Clinical and Laboratory Standards Institute guideline (CLSI) guidelines M44-A. Further analysis was done for potential risk factors and compared between culture positive and negative patients.
RESULTS: Of 150 patients recruited, the majority ($n = 27$) were between 51 and 60 years and the male to female ratio was 1.63:1. Fifteen patients (10%) were culture positive. The culture positivity was significantly higher in acute lymphocytic leukemia (ALL) than in non-ALL patients ($p = 0.03$). There was significant association of candidaemia with leucopenia, chemotherapeutic drugs, corticosteroids and presence of indwelling devices. Duration of disease ($p = 0.032$) and duration of hospitalization ($p = 0.003$) were significantly prolonged in culture positive patients. *C. tropicalis* was the commonest isolate (46.67%), with non- Candida albicans outnumbering *C. albicans* in all categories of hematological malignancies (2.75:1). All isolates of *C. albicans* were uniformly sensitive to all the azoles, but only 50% were sensitive to amphotericin B and none to nystatin and flucytosine.
CONCLUSIONS: This observational study identifies ALL and chronic lymphocytic leukemia (CLL) as the forms of hematological malignancy predominantly associated with candidemia; specifies risk factors and chemotherapeutic agents predisposing patients towards its occurrence; reports a preponderance of *C. tropicalis* among the causative agents and finds voriconazole to be the most effective antifungal agent against the recovered isolates. This information could assist in tailoring prophylactic and therapeutic antifungal practices for this infection, according to local epidemiological and mycological characteristics.

KEYWORDS: Hematological malignancies; Candida infections; Antifungal resistance; *Candida tropicalis*; Non-*Candida albicans*

The threat of opportunistic *Candida* infections has been increasing in contemporary health care scenarios,[1–4] with patients suffering from hematological malignancies being particularly vulnerable to such infections.[5–7] Apart from being widely prevalent, opportunistic *Candida* infections are often acutely progressive, difficult to diagnose, and are associated with increased hospital stays and high mortality rates.[3] Antifungal resistance, which has arisen because of the increasing prophylactic use of fluconazole and the relative rise in the proportion of non-*Candida albicans* species, has also been evolving lately as a major challenge in the management of *Candida* infections.[2,8–10] The increasing isolation of non-C. *albicans* infections earlier during the course of cytotoxic chemotherapy[11] necessitates an evaluation of the antifungal susceptibility profile of *Candida* isolates, to ensure the optimal choice of prophylactic and therapeutic antifungal agents in patients with hematological malignancies.

Although India has a high prevalence of opportunistic *Candida* infections, representative data on the epidemiological and mycological characteristics of these infections are virtually nonexistent in vast stretches of the country. Moreover, owing to the geographical and temporal variation often observed in the distribution of *Candida* species, there is a need to investigate and monitor local epidemiological patterns of candidemia in the context of the immense ecogeographical diversity observed in India. In our previous study on the profile of *Candida* infections in adult intensive care unit (ICU) patients, we have observed ongoing cancer chemotherapy to be an important risk factor for the development of candidemia at our center.[12] In view of this initial observation and considering the paucity of data from Indian centers on this subject, we undertook this study with the objective of exploring the epidemiological and mycological characteristics of candidemia occurring in patients suffering from hematological malignancies, and thereby ascertaining the contributing risk factors and determining the antifungal susceptibility profile of the recovered *Candida* isolates.

MATERIALS AND METHODS

This prospective observational study was conducted on consecutive patients suffering from hematological malignancy who reported to the Medical Oncology Unit of a tertiary-care teaching hospital in the Himalayan region of northern India with a febrile episode during the 18-month study period, from November 2010 to April 2012. A febrile episode was defined, for the purpose of this study, by a recorded oral temperature exceeding 38 °C (100.4°F) in a patient presenting with febrile symptoms. A chemotherapeutic regimen was planned for every recruited patient for the management of the underling hematological malignancy and the patients were advised to report to the hospital for their scheduled courses of chemotherapy/radiotherapy or following the development of any emergency condition. Monitoring of disease activity and chemotherapy-related adverse effects was done at every scheduled visit, according to standard guidelines, using blood counts, liver function tests, kidney function tests, bone marrow examination, and imaging wherever required. The febrile episode was investigated for the development of candidemia by performing blood culture. Single blood samples (5 mL in case of adults and 2 mL in case of children) were drawn with proper aseptic precautions and inoculated into biphasic brain heart infusion medium. The blood culture bottles were incubated for 7 days at 25 °C and were tilted for half an hour every day until the appearance of fungal colonies on the solid phase. Isolates recovered were subcultured on Sabouraud's dextrose agar (SDA) and typical *Candida* colonies, characterized by smooth, creamy, and pasty appearance on SDA, were speciated using standard tests such as germ tube test, sugar assimilation test, sugar fermentation test, microscopic morphology on corn meal agar, and color production on CHROMagar media. Recovery of any *Candida* species from blood cultures was taken as evidence of candidemia. The *Candida* isolates were also subjected to antifungal susceptibility testing using the disk diffusion method on Müller–Hinton agar with 2% glucose and 0.5 μg/mL methylene blue, according to the Clinical and Laboratory Standards Institute guideline M-44A.[13] Susceptibility testing was performed with commercially procured antifungal disks (HiMedia, Mumbai, India) against fluconazole (25 μg), clotrimazole (10 μg), voriconazole (1 μg), amphotericin B (100 U), nystatin (50 μg), and flucytosine (1 μg). For interpretation of sensitivity, zone sizes recommended by disk manufacturers were considered. American Type Culture Collection (ATCC) strains C. *albicans* 90028, *Candida parapsilosis* 22019, and *Candida krusei* 6258 were used as controls.

The study protocol was reviewed and approved by the Institutional Ethics Committee and written informed consent was recorded from each of the recruited patients.

Statistical analysis

A web-based calculator (http://www.stat.ubc.ca/~rollin/stats/ssize/) was used for calculating sample size. We presumed a candidemia prevalence of 1–6% in the population and aimed at detecting an approximate difference of 5% in the prevalence of candidemia in patients with hematological malignancies, with a desired power of 0.8 and α value of .05. The optimal sample size calculated was between 53 and 172. The Chi-square test was used for comparing categorical variables and the independent *t* test was used for comparing continuous variables between candidemic and noncandidemic cases. Mean, standard deviation (SD), and odds ratio were calculated according to standard definitions. SPSS version 21.0 (SSPS Inc., Chicago, IL, USA) was used for analysis and $p < .05$ was considered significant.

RESULTS

A total of 150 patients (93 men) were recruited to this study. The mean (±SD) age of the study group was 40 (±21) years. The majority of the patients ($n = 27$; 15 men) were between 51 and 60 years of age and 16 patients (10.66%; 10 men) were in the 1st decade of life. Seven forms of hematological malignancy were observed among the recruited patients, with acute leukemia being the predominant form ($n = 75$). Among patients with acute leukemia, 39 (26%) were suffering from acute myeloid leukemia (AML) and 36 (24%) had acute lymphocytic leukemia (ALL).

Fifteen patients (10 men) had positive culture for candidemia, thereby recording a prevalence of 10% candidemia cases among febrile patients with hematological malignancy. The mean (±SD) age of the culture-positive candidemic patients was 30 (±23) years. No significant difference was observed in the age and sex distribution of culture-positive and culture-negative patients. However, culture positivity for candidemia was significantly higher among ALL patients (odds ratio = 3.2; $p = .03$). Candidemia was not observed among patients with multiple myeloma ($n = 14$) and Hodgkin's lymphoma ($n = 4$; Table 1).

We next sought to determine the risk factors that predisposed the patients with hematological malignancy for candidemia. We observed a significantly higher proportion of leukopenia (white blood cell count < 4000 cells/mm^3) among candidemic patients (odds ratio = 7.3; $p = 0.00015$). Among iatrogenic factors, administration of chemotherapeutic drugs (odds ratio = 16.1; $p = 0.0066$), use of corticosteroids (odds ratio = 4.7; $p = 0.003892$), and presence of indwelling devices such as urinary catheter, central venous catheter, and nasogastric tube (odds ratio = 4.6, $p = 0.0038$; odds ratio = 4.5, $p = 0.015$; and odds ratio = 6.8, $p = 0.023$, respectively) were also found to be significantly common among the culture-positive patients. Duration of disease ($p = 0.032$) and duration of hospitalization ($p = 0.003$) were also significantly prolonged in culture-positive patients (Table 2).

We also explored the possible association of different chemotherapeutic regimens with the occurrence of candidemia. The recruited patients in our study received a total of 13 chemotherapeutic regimens, of which there was one regimen for AML; three regimens for ALL; two each for chronic lymphocytic leukemia (CLL), chronic myeloid leukemia, non-Hodgkin's lymphoma, and multiple myeloma; and one regimen for Hodgkin's lymphoma. Four of these 13 regimens were found to be significantly associated with candidemia in our patients. The regimens found to be associated with candidemia were (a) cytosine

Table 1. Distribution of candidemic patients across the spectrum of hematological malignancies.

Hematological malignancy	No. of patients	No. of candidemic patients (%)	*p*
Acute lymphocytic leukemia	36	7 (19.44)	0.03
Chronic lymphocytic leukemia	13	2 (15.38)	0.49
Acute myeloid leukemia	39	3 (7.69)	0.57
Non-Hodgkin's lymphoma	26	2 (7.69)	0.66
Chronic myeloid leukemia	18	1 (5.55)	0.50
Multiple myeloma	14	0	0.19
Hodgkin's lymphoma	04	0	0.49
Total	150	15 (10)	

Table 2. Distribution of potential risk factors among the recruited patients.

Risk factors	Total No. of patients		Candidemic patients		*p*
	Present (%)	Absent (%)	Present (%)	Absent (%)	
Leukopenia	39 (26)	111 (74)	10 (66.67)	5 (33.33)	0.00015
Neutropenia	100 (66.67)	50 (33.33)	12 (80)	3 (20)	0.24
Anemia	77 (51.33)	73 (48.67)	9 (60)	6 (40)	0.47
Steroids	50 (33.33)	100 (66.67)	10 (66.67)	5 (33.33)	0.00389
Chemotherapy	104 (69.33)	46 (30.66)	15 (100)	0	0.0066
Radiotherapy	16 (10.67)	134 (89.33)	2 (13.33)	13 (86.67)	0.72
Indwelling devices					
IVC	74 (49.33)	76 (50.67)	8 (53.33)	7 (46.67)	0.74
Urinary catheter	35 (23.33)	115 (76.67)	8 (53.33)	7 (46.67)	0.0038
CVC	14 (9.33)	136 (90.67)	4 (26.67)	11 (73.33)	0.015
Nasogastric tube	5 (3.33)	145 (96.67)	2 (13.33)	13 (86.67)	0.023
Parenteral nutrition	18 (12)	132 (88)	3 (20)	12 (80)	0.31

CVC = central venous catheter; IVC = intravenous catheter.

arabinoside and daunorubicin (AML; odds ratio = 4.0, $p = .047$); (b) cyclophosphamide and/or vincristine, doxorubicin/daunorubicin, L-asparaginase, and prednisolone (ALL; odds ratio = 4.1, $p = 0.023326$); (c) mercaptopurine and prednisolone (ALL; odds ratio = 10.2, $p = 0.006873$); (d) cyclophosphamide, vincristine, and prednisolone (CLL; odds ratio = 6.8, $p = 0.022$). Studying the association with individual chemotherapeutic drugs, we observed significantly higher occurrence of candidemia following the use of cyclophosphamide (odds ratio = 3.8, $p = 0.01096$), vincristine (odds ratio = 4.0, $p = 0.0086$), L-asparaginase (odds ratio = 4.1, $p = 0.023$), doxorubicin (odds ratio = 3.4, $p = 0.025$), and mercaptopurine (odds ratio = 4.1, $p = 0.0068$).

Candida tropicalis was the most common isolate recovered in our study (46.67%), with non-*C. albicans* outnumbering *C. albicans* in all categories of hematological malignancies (2.75:1). *C. tropicalis* was the only species of *Candida* isolated from patients with AML and chronic myeloid leukemia. Apart from *C. tropicalis* and *C. albicans*, one isolate each of *Candida glabrata*, *C. krusei*, *C. parapsilosis*, and *Candida dubliniensis* were recovered from the patients. Because *C. krusei* is intrinsically resistant to azoles, it was not analyzed for sensitivity to the azole group of drugs. While all isolates of *C. albicans*, *C. parapsilosis*, and *C. dubliniensis* were uniformly sensitive to all the azoles tested, one isolate (14.3%) of *C. tropicalis* was resistant to fluconazole and clotrimazole. Sensitivity to voriconazole was also observed for all the isolates, apart from *C. glabrata* (Table 3). Quality control of the used ATCC strains was performed by determining their minimum inhibitory concentration (MIC) to the antifungal agents used in the study. *C. parapsilosis* 22019 demonstrated MIC of 0.25–1.0 µg/mL for amphotericin B, 0.12–0.5 µg/mL for flucytosine, 2.0–8.0 µg/mL for fluconazole, and 0.016–0.064 µg/mL for voriconazole. The corresponding MIC ranges for *C. krusei* ATCC 6258 were 0.5–2.0 µg/mL, 4.0–16 µg/mL, 16.0–64.0 µg/mL, and 0.06–0.25 µg/mL.

DISCUSSION

In this paper, we report a prevalence of 10% for candidemia among febrile hematological malignancy patients attending a tertiary-care teaching hospital in the Himalayan region of northern India. Among the various forms of hematological malignancy, we observed a significantly higher predisposition to candidemia in ALL. We also specify risk factors and chemotherapeutic regimens significantly associated with the occurrence of candidemia in these patients. *C. tropicalis* was the commonest species recovered in our patients and voriconazole was the most effective antifungal agent.

Table 3. Results of antifungal susceptibility tests by disk diffusion method.

Isolates	No. (%)	Sensitive (%)					
		Flu	Cc	Vo	5-FC	Nys	AmpB
Candida albicans	4 (26.7)	4 (100)	4 (100)	4 (100)	0	0	2 (50)
Candida tropicalis	7 (46.7)	6 (85.7)	6 (85.7)	7 (100)	0	3 (42.9)	7 (100)
Candida glabrata	1 (6.7)	0	0	0	0	0	0
Candida parapsilosis	1 (6.7)	1 (100)	1 (100)	1 (100)	0	0	1 (100)
Candida krusei	1 (6.7)	0	0	0	0	1 (100)	0
Candida dubliniensis	1 (6.7)	1 (100)	1 (100)	1 (100)	0	1 (100)	1 (100)

5-FC = 5-flucytosine; AmpB = amphotericin B; Cc = clotrimazole; Flu = fluconazole; Nys = nystatin; Vo = voriconazole.

The prevalence of candidemia among patients with hematological malignancy has been found to vary widely between 1.6% and 22.9%[5,14–16] depending on the patient profile studied, geographical location involved, and diagnostic criteria used. Although there have been reports from Indian centers on the spectrum of bacterial infections occurring in hematological malignancies,[17,18] these did not report the epidemiological and mycological characteristics of candidemia. Our findings, with regard to the increased occurrence of candidemia in acute leukemia patients, are consistent with previous reports from other centers across the globe.[5,19,20] However, the relatively high frequency of candidemia observed in this study in CLL patients was not in sync with earlier studies.[5] This relatively high frequency could be due to late presentation of such patients in our population, which could lead to myelophthisis and subsequent neutropenia. Several risk factors identified by us, namely, leukopenia, presence of indwelling devices, use of corticosteroids, have also been previously reported in earlier studies to be significantly associated with candidemia in patients with hematological malignancies.[14,15,19,21,22] However, to the best of our knowledge, this is the first study to have evaluated the relative risk of candidemia associated with individual chemotherapeutic regimens administered in hematological malignancies. Mucosal damage, due to anticancer chemotherapy, is considered to be a major factor contributing to invasive candidiasis originating from the gastrointestinal tract.[23] Identification of specific chemotherapeutic regimens, which add to the vulnerability to candidemia, could help in risk stratification and decision making regarding use of empirical antifungal prophylaxis in selected subsets of patients.

Geographical variation is an important feature in the species distribution of *Candida*. In accordance with trends observed in majority of studies across the globe,[24–30] shift in the species distribution of *Candida* has been noted in several major Indian hospitals. Non-*C. albicans* have been isolated from 30% to 90% of invasive candidiasis cases.[26–32] However, in recent studies from our center conducted on adult and neonatal ICU patients, we have observed a predominance of *C. albicans* among the recovered isolates.[12,33] The finding of *C. tropicalis* being the most frequently recovered species in this study is indicative of a unique mycological trait specific to the epidemiology of candidemia in hematological malignancies. Interestingly, previous papers have reported *C. tropicalis* to be a common isolate in hematological malignancies, with *C. albicans* being more frequently observed in patients with solid organ tumors.[34] Moreover, similar to our findings, other studies from India, Singapore, and Taiwan have reported *C. tropicalis* to be the commonest non-*C. albicans* species[35–37]; by contrast, *C. glabrata* is reported to be the commonest non-*C. albicans* species isolated from the rest of the world.[24,32,38–40]

The prophylactic use of fluconazole is a standard practice in hematological malignancy patients undergoing chemotherapy and most of the patients recruited in this study were receiving antifungal prophylaxis. This could be a cause for the species shift toward non-albicans candidemia and the alarming degree of antifungal resistance observed in our study.

Our study suffered from several limitations. First, because we used culture positivity in brain heart infusion broth as the criterion for diagnosing candidemia, the estimated prevalence of 10% could be an underassessment of the actual prevalence. Employing

more sensitive systems such as automated blood culture techniques or use of novel biomarkers (e.g., 1,3-β-D-glucan) might have resulted in a higher diagnostic yield. Second, the relatively small number of patients in some of the subgroups of hematological malignancy (e.g., Hodgkin's lymphoma) makes our study inadequately powered to assess the actual prevalence of candidemia in these subgroups. Third, the relatively less number of *C. albicans* isolates could lead to seemingly high proportion of resistance to amphotericin B. Finally, we did not test our isolates for susceptibility to echinocandins, primarily because this group of antifungal agents was not in use at our center due to affordability issues.

CONCLUSION

We observe that this observational study identifies ALL and CLL as the forms of hematological malignancy predominantly associated with candidemia. In addition, risk factors and chemotherapeutic agents predisposing patients toward its occurrence were specified. We have also noted a preponderance of *C. tropicalis* among the causative agents and identified voriconazole to be the most effective antifungal agent against the recovered isolates. This study could assist in alerting clinicians about the prevalence of candidemia in hematological malignancy and also in tailoring prophylactic and therapeutic antifungal practices, according to local epidemiological and mycological characteristics.

CONFLICTS OF INTEREST

All contributing authors declare no conflicts of interest.

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